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CONTENTS

Structure and metabolism of peptidoglycan and molecular requirements allowing its detection by the *Drosophila* innate immune system

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Peptidoglycan (murein) is a major essential and specific constituent of the bacterial cell wall. Its main function is to protect cells against the internal osmotic pressure and to maintain the characteristic cell shape. It also serves as a platform for the anchoring of specific proteins and other cell wall components. This giant macromolecule is composed of long glycan chains cross-linked by short peptides. Any alteration of the disaccharide–peptide basic unit results in a global change of peptidoglycan structure and properties. Such global variations are encountered in nature as conserved variations along phyletic lines but have sometimes been acquired as a result of mutations or as a mechanism of resistance against cell-wall targeted antibiotics. During bacterial cell growth and division, the peptidoglycan mesh is constantly broken down by a set of highly specific hydrolases in a maturation process allowing insertion of newly synthesized units in the pre-existing polymerized material. Depending on the bacterial species considered, degradation fragments are either released in the growth medium or efficiently re-utilized for synthesis of new murein in a sequence of events termed the recycling pathway. Peptidoglycan is one of the main pathogen-associated molecular patterns recognized by the host innate immune system. Variations of the structure and metabolism of this cell wall component have been exploited by host defense mechanisms for detection/identification of invading bacterial species. Modification of the peptidoglycan structure could also represent a mechanism allowing bacteria to escape these host defense systems.

Keywords: Bacterial cell wall, peptidoglycan, murein, innate immunity, peptidoglycan recognition proteins, antibiotics

Structure and function of peptidoglycan

Peptidoglycan (murein sacculus) is an essential and specific component of the bacterial cell wall.[1,2] This giant (cell-sized) and rigid structural macromolecule is of fundamental importance since it protects cells against the effects of the internal osmotic pressure. Indeed, any inhibition of its biosynthesis (mutation, antibiotic, *etc.*) or its specific degradation (*e.g.* lysozyme) during cell growth irremediably results in cell lysis. Peptidoglycan also contributes to the characteristic cell shape and serves as a scaffold for anchoring other cell envelope components, including proteins[3,4] and polysaccharides.[5] It is a complex heteropolymer consisting of long polysaccharide chains made of alternating *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc) residues linked β-1→4, which are cross-linked through short peptides. The peptides exhibit some specific and unusual features such as the occurrence of alternating D- and L-isomers of amino acids, a γ-bonded D-glutamic acid, and non-protein amino acids such as diaminopimelic acid (DAP), lanthionine or ornithine. In *Escherichia coli*, the structure of the repeating 'muropeptide' unit is mainly

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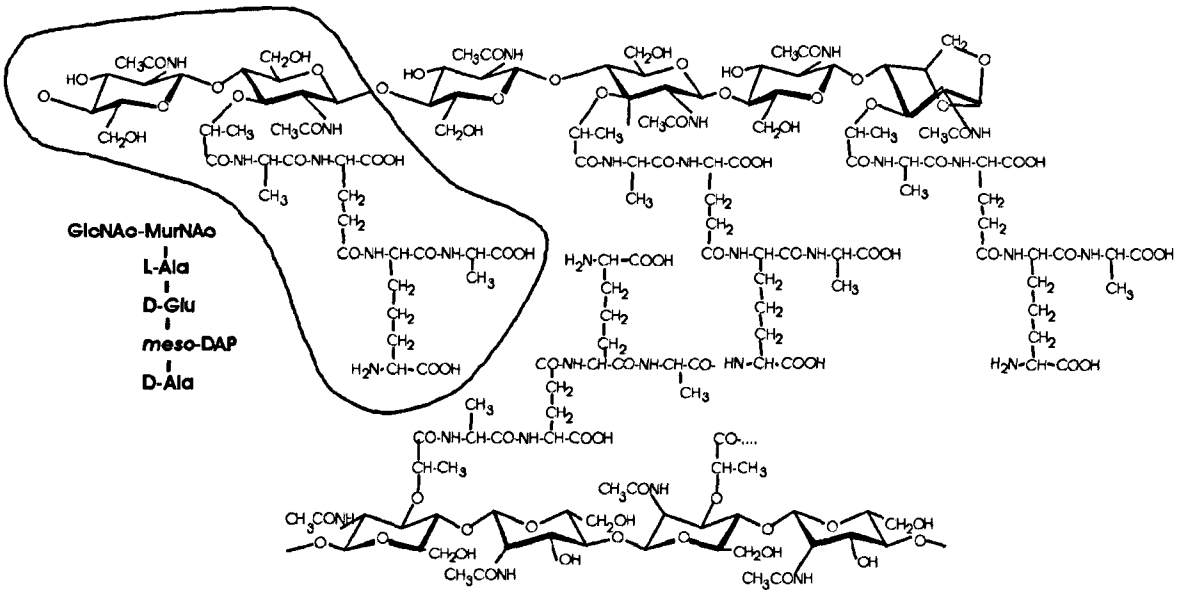

Fig. 1. Structure of the peptidoglycan of *Escherichia coli*.

GlcNAc-MurNAc-L-Ala-γ-Glu-*meso*-DAP-D-Ala, with some variations, as described below, and the terminal MurNAc residue at the end of each glycan strand is present in a non-reducing 1,6-anhydro form (Fig. 1). Most of the cross-links between glycan strands extend from the carboxyl group of a D-Ala residue in position 4 of one stem peptide to the free amino group of a DAP residue in position 3 of an adjacent stem peptide (D–D bond). These different characteristics make this polymer specific of the bacterial world and resistant to classical proteases. Based on the DAP content and size, the murein sacculus of *E. coli* is believed to consist of a single sheet of peptidoglycan, representing about 1% of bacterial cell dry weight (~3–5 million of muropeptide equivalents per cell, depending on growth conditions and cell size).[2,6]

Biosynthesis of peptidoglycan

The biosynthesis of peptidoglycan is a complex two-stage process (Fig. 2).[7] The first stage involves the assembly of the basic monomer unit by enzymes located in the cytoplasm or at the inner side of the cytoplasmic membrane. Its initial nucleotide precursor, UDP-GlcNAc, which is shared with other pathways, is synthesized in four steps from fructose-6-P and used by the MurA and MurB enzymes to generate UDP-MurNAc. The step-wise formation of the peptide moiety is then performed by a series of enzymes designated as the Mur synthetases (MurC,D,E,F) which are responsible for the successive additions of L-Ala, D-Glu, *meso*-DAP and D-Ala-D-Ala onto UDP-MurNAc.[7] The high substrate specificity of these enzymes is the main factor ensuring that the structure of the end product, UDP-MurNAc-pentapeptide, is correct. The phospho-MurNAc-pentapeptide and GlcNAc moieties are then successively transferred onto the undecaprenyl phosphate carrier lipid (C_{55}-P) by two membrane enzymes, the MraY translocase and MurG transferase, resulting in the formation of GlcNAc-MurNAc-(pentapeptide)-PP-undecaprenol, the lipid II intermediate.[7] The second stage involves the transfer of lipid II to the outer side of the cytoplasmic membrane, by a yet unknown mechanism, and its polymerization by transglycosylases and transpeptidases activities, both of which are mainly supported by the well-known penicillin-binding proteins (PBPs).[8] Conditional-lethal mutations affecting the biosynthesis of peptidoglycan, as well as different classes of antibiotics interfering with some of its steps, have been described, most of which had a cell lytic effect. The actual serious health problem raised by the emergence of antibiotic multi-resistant pathogenic bacteria explains the renewed interest for these different enzymes considered as interesting potential targets for the search for new antibiotics.

Maturation and recycling of peptidoglycan

The stress-resistant cell wall is, however, not a static structure. The remodeling and enlargement of this network which necessarily occurs during cell growth and division is believed to result from a balanced functioning of murein-degrading and murein-synthesizing activities, the former generating transient breaks in the 'old' structure to allow insertion of nascent incoming peptidoglycan material (Fig. 2). In *E. coli*, as many as 18 murein hydrolases have been identified, belonging to six different families which include lytic transglycosylases, amidases and endopeptidases, a specific hydrolase existing for

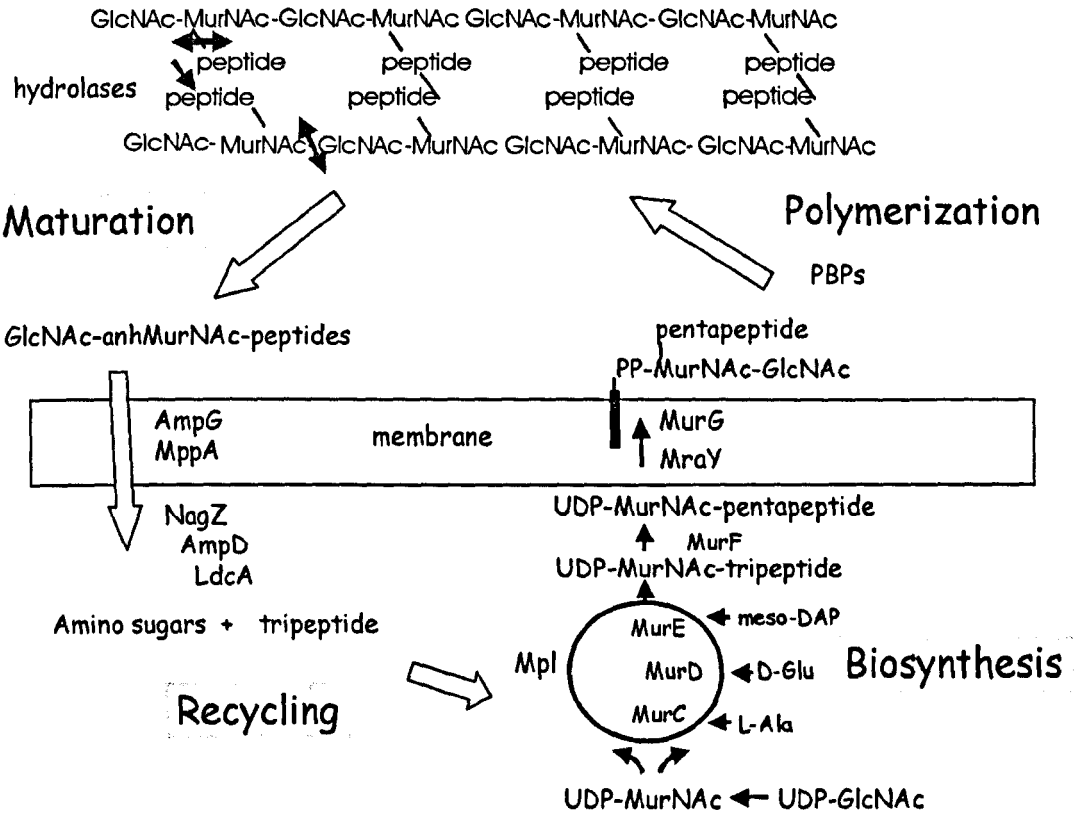

Fig. 2. Metabolism of peptidoglycan in *Escherichia coli*. Cytoplasmic and membrane enzymes (Mur synthetases, MraY, murG) catalyze the stepwise formation of the peptidoglycan lipid intermediate II, which consists in the disaccharide-pentapeptide unit linked onto the undecaprenyl phosphate (C_{55}-P) carrier lipid. This motif is then translocated to the outer side of the inner membrane where polymerization reactions (transglycosylation and transpeptidation) catalyzed by penicillin-binding proteins take place. During growth and division, an important and permanent remodeling of the peptidoglycan structure occurs that is performed by multiple specific hydrolases. This results in a dramatic turnover of the macromolecule and the release of fragments, most of which being efficiently re-imported in the cytoplasm, maturated, and re-used for *de novo* peptidoglycan synthesis by a dedicated set of recycling enzymes.

almost each covalent bond in the murein.[9] Lytic transglycosylases such as the soluble SltY enzyme are of special interest: as do lysozyme and muramidases, they cleave the β-1,4-glycosidic bond between MurNAc and GlcNAc and are able to totally degrade intact murein *in vitro* but, unlike the latter, they concomitantly catalyze the formation of an intramolecular bond between C-1 and C-6, resulting in a non-reducing 1,6-anhydro-MurNAc residue (anhMurNAc). The remodeling of the murein by these different hydrolases (autolysins) results in a dramatic turnover phenomenon, estimated at 40–50% per generation time. The release of cell wall peptides in the growth medium was observed during this process.[10] The main intracellular turnover products were identified as GlcNAc-anhMurNAc-tetra- and -tripeptides. The latter compounds are imported in the cytoplasm by a specific permease (AmpG) and efficiently re-used in a process that has been termed the recycling pathway (Fig. 2).[11,12] This process involves a large set of enzymes (amidase AmpD, L,D-carboxypeptidase LdcA, β-*N*-acetylglucosaminidase NagZ) that catalyze the stepwise break down of anhydro-muropeptides to yield GlcNAc, anhMurNAc, D-Ala and murein tripeptide (L-Ala-γ-D-Glu-*meso*-DAP).[13–16] Murein tripeptide is then directly ligated to UDP-MurNAc by a dedicated Mur synthetase, Mpl, and thus re-enters the biosynthetic pathway for *de novo* peptidoglycan synthesis.[17] The two amino sugars are also re-used and re-injected in the general metabolism.[18]

Diversity of the peptidoglycan structure in the bacterial world

Variations in the structure of peptidoglycan are encountered mainly in the sequence of the stem peptides.[19] The greatest variation is at position 3 since, up to now, about 10 different amino acids have been detected in this position, *meso*-DAP and L-Lys being the most frequent. Partial to total replacement of L-Ala at position 1 by Gly or Ser, or D-Ala at position 5 by D-lactate or D-Ser, have been reported in some species. The α-carboxyl group of D-Glu and the ε-carboxyl group of DAP are often amidated (but not in *E. coli*). The above described structure and composition of *E. coli* peptidoglycan (DAP-type) is

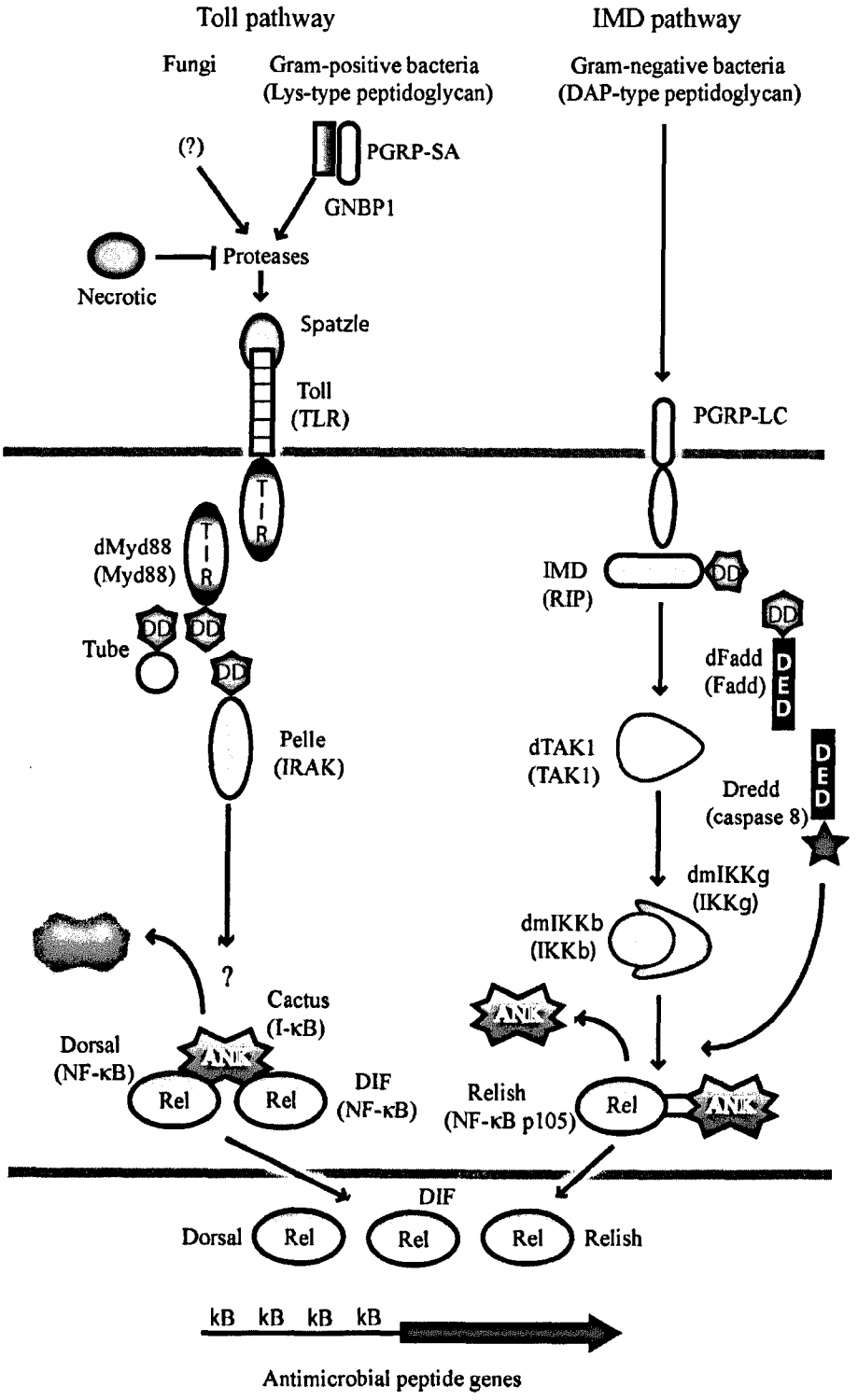

Fig. 3. The Toll and Imd pathways. Antimicrobial peptide genes are regulated by a balance between two signaling pathways: the Toll pathway that is largely activated by fungi and Gram-positive bacteria, and the Imd pathway that is mainly activated by Gram-negative bacteria. According to the κB sites present in their promoters, antimicrobial peptide genes are more sensitive to either the Toll cascade (*e.g. Drosomycin*), the Imd cascade (*e.g. Diptericin*), or are co-regulated. The Toll receptor is activated upon binding with a cleaved form of Spätzle that is processed by proteolytic cascades activated by secreted recognition molecules (PGRP-SA, GNBP1). PGRP-SA may bind to Lys-type peptidoglycan found in Gram-positive bacteria. Toll activates an intracellular signal transduction pathway that regulates the nuclear translocation of the NF-κB proteins Dif and Dorsal. The Imd pathway is probably triggered by an interaction between the transmembrane receptor, PGRP-LC, and DAP-type peptidoglycan from Gram-negative bacteria. Following PGRP-LC activation, the death domain adapter protein, Imd, is recruited and binds to dFadd which interacts with the caspase Dredd. Dredd has been shown to associate with Relish which it might cleave directly, after Relish is phosphorylated by the *Drosophila* IKK complex. The dmIKK complex is itself activated by the MAPKKK dTAK1 in an Imd-dependent manner. After cleavage, the Relish Rel domain moves to the nucleus where it regulates immune target genes. The Toll and Imd cascades share striking homology with pathways that regulates NF-κB innate immune response in vertebrates (homologues are indicated within the bracket).

shared by nearly all Gram-negative bacteria as well as by some Gram-positive rods.[19,20] The situation is more complex in many Gram-positive organisms (mostly Lys-type) in which additional interpeptides are required for the cross-linking of the peptidoglycan stem peptides.[19] The structure of these additional side chains, L-Ala_2, L-Ser-L-Ala, Gly_5, D-Asx *etc.*, varies from one organism to the other. They are added to the stem peptide unit at the level of UDP-MurNAc-pentapeptide, or of the lipid intermediates, by additional specific enzymes.[21–23] When compared, the glycan part of peptidoglycan is rather uniform but could also exhibit few variations, such as acetylation or phosphorylation of hydroxyl groups of MurNAc, the occasional absence of *N*-acyl or peptide substituents, or the replacement of MurNAc by its *N*-glycolyl derivative, as observed in mycobacteria. The structure of the peptidoglycan is usually determined by HPLC analysis of the pattern of muropeptides released after muramidase digestion of isolated sacculi.[24,25]

Flexibility and acquired modifications of the peptidoglycan structure

The peptidoglycan of a given bacteria can undergo important structural modifications in a variety of circumstances (growth conditions, antibiotic treatments, mutations). For instance, total or partial replacement in this structure of *meso*-DAP by different analogues (lanthionine, cystathionine, LL-DAP) has been demonstrated in *dap* mutant strains,[26–28] and the toxic incorporation of L-Lys at the same position was observed following overexpression of the *Staphylococcus aureus* L-Lys-adding MurE enzyme in *E. coli* cells.[29] Resistance to antibiotics targeting the peptidoglycan pathway could arise by modification of the peptidoglycan structure. Vancomycin is a glycopeptide antibiotic which tightly binds to the terminal D-Ala-D-Ala motif of the lipid II intermediate, thereby inhibiting subsequent polymerization steps. Natural or acquired resistance to this antibiotic was described in strains synthesizing precursors with either D-lactate or D-Ser replacing D-Ala at position 5 of the peptide,[30,31] whose affinity for the glycopeptide is much lower. Mutations resulting in a modification of the composition of the interpeptide bridges or in a by-pass of the essential PBPs by L,D-transpeptidation in Gram-positive species were also shown to modify the susceptibility of strains to β-lactams.[23,32–34] Morphological transition of *Helicobacter pylori* from spiral to coccoid was also correlated with a modification of the structure of its cell wall.[35] Also, *O*-acetylation of MurNAc or *N*-deacetylation of GlcNAc were shown to increase resistance of pathogenic bacteria to lysozyme, an important host defense component.[36,37] Finally, modifications of the peptidoglycan structure of pathogenic bacteria are also expected to occur in the course of host infection. In particular, overexpression of the activity of some of the peptidoglycan hydrolases has been demonstrated during cell invasion by *Shigella flexneri* and *Salmonella typhimurium*.[38,39]

Recognition of specific peptidoglycan motifs by the Drosophila *innate immune system*

Innate immunity is a first line of defense against invading pathogenic bacteria. The response is initiated following recognition by host receptors of highly conserved molecules that are exclusively encountered in bacteria, such as lipopolysaccharides and peptidoglycan. Recent work showed that *Drosophila* uses two distinct signaling cascades, the Toll and Imd pathways, to sense and respond specifically to invasion by Gram-positive and Gram-negative bacterial species (Fig. 3). Microbial recognition acting upstream of the Toll and Imd pathways is achieved through peptidoglycan recognition proteins (PGRPs). PGRPs can bind to peptidoglycan and are found in many species including insects and mammals.[40–42] In *Drosophila*, 13 *PGRP* genes have been identified,[43] two of which are currently implicated in the immune response: (i) an extracellular recognition factor, PGRP-SA, activates the Toll pathway in response to Gram-positive bacteria;[44] and (ii) a putative transmembrane protein, PGRP-LC, acts upstream of the Imd pathway.[45–47] Interestingly, Gram-negative DAP-type peptidoglycan, but not LPS, is the most potent inducer of the PGRP-LC/Imd pathway while the PGRPSA/Toll pathway is predominantly activated by Gram-positive Lys-type peptidoglycan. Therefore, *Drosophila*'s ability to discriminate between Gram-positive and Gram-negative bacteria does not rely on lipopolysaccharide detection but rather on the recognition of specific forms of peptidoglycans.[48,49]

Interestingly, two signatures of Gram-negative bacteria peptidoglycan, the presence of DAP in the peptide stem and of anhMurNAc in the glycan chain, allow discrimination between Gram-negative and Gram-positive bacteria.[50] Peptidoglycan oligomerization also plays a role in Imd and Toll activation. Together, these results indicate the existence of multiple requirements for efficient peptidoglycan recognition by the fly immune system. This and recent observations indicating that peptidoglycan recognition in mammals is mediated by Nod, but not by Toll-like receptors, via the detection of small muropeptide fragments demonstrate that peptidoglycan is a complex immune elicitor.[51–53] Additional host factors may be involved in peptidoglycan recognition participating either upstream in the degradation of cell wall compounds and peptidoglycan transport, or downstream in the degradation of microbial ligands. Interestingly in this respect, peptidoglycan degrading activities,

of either amidase or L,D-carboxypeptidase type, were recently demonstrated or at least suggested for several PGRPs.[54-56] Enzymes from the microbe may modulate the course of infection by modifying the peptidoglycan structure or controlling their release. Thus, peptidoglycan recognition is emerging as a multi-step and complex process.

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